CARBAMATE INSECTICIDES

Schiff Base Phenyl N-Methylcarbamates

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A new series of phenyl carbamates with a *p*-imino group (Schiff bases) has been prepared. Derivatives containing the imino group in the para position and small alkyl groups in the meta position have shown interesting insecticidal activity in screening tests with Mexican bean beetles and Southern armyworms.
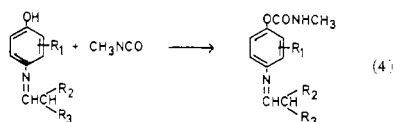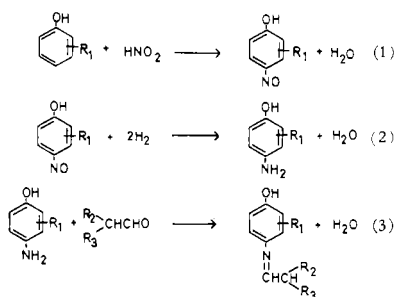
A PREVIOUS paper (7) described the synthesis and insecticidal activity of a number of phenyl *N*-methylcarbamates. Interesting activity was observed when the aromatic ring was substituted with small alkyl and alkylamino groups in the meta and para positions.

The addition of the alkylamino group to the aromatic ring contributed to a considerable increase in insecticidal potency. It was of interest to determine the effect of further changes in substituent groups attached to this nitrogen atom. Phenyl carbamates with a *p*-imino group (Schiff bases) were prepared and tested for insecticidal activity (6).

Synthesis

Phenols with the desired ortho and meta alkyl groups were used as the primary starting materials. The para nitrogen atom was introduced to the aromatic ring by nitrosation (Equation 1), nitration, or coupling with a diazonium salt. Any of these intermediates could be converted to the corresponding aminophenol by reduction. Catalytic reduction with hydrogen, assisted by a palladium catalyst, was especially convenient in the laboratory (Equation 2).
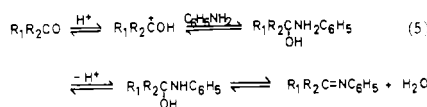
The Schiff bases were prepared by a reaction between the aminophenols and the corresponding aldehydes (Equation 3). The carbamate was subsequently synthesized by the base-catalyzed reaction between the Schiff base phenol and methyl isocyanate (Equation 4). Specific illustrations are described in more detail below.

$$OH / R_1 + HNO_2 \longrightarrow OH / R_1, NO + H_2O \quad (1)$$

$$OH / R_1, NO + 2H_2 \longrightarrow OH / R_1, NH_2 + H_2O \quad (2)$$

$$OH / R_1, NH_2 + \underset{R_3}{\overset{R_2}{}}CHCHO \longrightarrow OH / R_1, N=CH\underset{R_3}{\overset{R_2}{}} + H_2O \quad (3)$$

$$OH / R_1, N=CH\underset{R_3}{\overset{R_2}{}} + CH_3NCO \longrightarrow OCONHCH_3 / R_1, N=CH\underset{R_3}{\overset{R_2}{}} \quad (4)$$

R_1 = ortho or meta alkyl groups

R_2, R_3 = small aliphatic hydrocarbon groups

The simplest derivative in this series would result from the combination of formaldehyde and *p*-aminophenol to give *p*-methylideneaminophenol as the carbamate precursor. However, only tars and polymers could be isolated when this was attempted, because of the high susceptibility of this simple imine group to condensation and polymerization reactions (12). Isopropylideneaminophenol (4, 5) had been prepared and characterized, but had a pronounced tendency to decompose by acid hydrolysis. Moderate stability was observed for *p*-isobutylideneaminophenol and related homologs containing additional methylene groups.

A mechanism (10) for the production of Schiff bases proposes that the carbonyl group is protonated to give a carbonium ion which rapidly adds to the amine (Equation 5).

$$R_1R_2CO \overset{H^+}{\rightleftharpoons} R_1R_2\overset{+}{C}OH \overset{C_6H_5NH_2}{\rightleftharpoons} R_1R_2\underset{OH}{C}NH_2C_6H_5 \quad (5)$$

$$\overset{-H^+}{\rightleftharpoons} R_1R_2\underset{OH}{C}NHC_6H_5 \rightleftharpoons R_1R_2C=NC_6H_5 + H_2O$$

The rate-determining step is the deprotonation of the nitrogen atom to give an unstable carbinolamine, which rapidly eliminates water to give the product. The reversibility of these reactions suggests an explanation for the observed instability of compounds of this type toward water. The effect of pH on this reaction has been investigated by Koehler, Sandstrom, and Cordes (9).

Since hydrolytic stability was presumed to be an essential property for a practical insecticide, efforts were concentrated on the preparation of derivatives which would not decompose on contact with water. Structural fea-

tures were sought which would prevent hydrolysis of the imino group. In fact, the phenolic Schiff base was synthesized in aqueous solution to preclude the preparation of unstable compounds. The carbamate ester group is also susceptible to hydrolysis, although the rate is slow in neutral solution.

It was observed that hydrolytic stability of the imino group was related to the steric configuration. Shielding by relatively large groups, attached to either the nitrogen or carbon atoms of the —N=C< group, or to both, produced stable Schiff bases which could be conveniently synthesized. Alkyl groups in the meta position appeared to be especially effective.
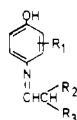
The Schiff base phenol precursors used for the preparation of the carbamates are summarized in Table I. The structures of new compounds were supported by means of elementary analysis and by an interpretation of their infrared and NMR spectra. A strong, sharp band in the 6-micron region, characteristic of the C=N stretching frequency, was present for every derivative.

The position of the imino group on the aromatic ring was determined by the nitrosophenol isomer formed during the reactions of the starting alkyl phenols with nitrous acid (Equation 1). The strong preference for nitrosation in the para position is well known (1, 11), even when it is hindered—for example, 3,5-diethylphenol was nitrosated exclusively in the para position (8).

In this laboratory, nitrosation and subsequent reduction of 3,5-xylenol produced the corresponding *p*-nitroso- and amino-3,5-xylenol with melting points which compared favorably with those found by Albert (1).

It was of interest to verify these general conclusions regarding isomer formation during nitrosation by interpretation of the NMR spectra of the product isolated. A Varian A-60 spectrometer was used with deuteroacetone as a solvent and tetramethylsilane as an internal reference. The ratios of the hydrogen

Table I. Schiff Base Phenols

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R_1	R_2	R_3	Molecular Formula	M.P., °C.	Found C	Found H	Found N	Theory C	Theory H	Theory N
H	CH_3	CH_3	$C_{10}H_{13}NO$	140–147[a]	71.85	7.63	8.53	73.59	8.03	8.58
H	CH_3	n-C_3H_7	$C_{12}H_{17}NO$	Oil	74.2	9.6	6.7	75.35	8.96	7.32
3,5-$(CH_3)_2$	CH_3	CH_3	$C_{12}H_{17}NO$	112	75.00	9.09	7.29	75.35	8.96	7.32
3,5-$(CH_3)_2$	C_2H_5	C_2H_5	$C_{14}H_{21}NO$	120–122	76.20	9.39	6.68	76.66	9.65	6.39
3,5-$(CH_3)_2$	CH_3	n-C_3H_7	$C_{14}H_{21}NO$	86–88	76.27	9.58	6.87	76.66	9.65	6.39
3,5-$(CH_3)_2$	C_2H_5	n-C_4H_9	$C_{16}H_{25}NO$	73–74	78.01	10.01	5.89	77.68	10.19	5.66
2,3-$(CH_3)_2$	CH_3	CH_3	$C_{12}H_{17}NO$	65–70	[b]					
3-CH_3-5-C_2H_5	C_2H_5	C_2H_5	$C_{15}H_{23}NO$	91–92	76.53	9.69	6.24	77.20	9.93	6.00
3-CN_3-5-C_2H_5	CH_3	n-C_3H_7	$C_{15}H_{23}NO$	64–65	77.22	9.78	6.32	77.20	9.93	6.00
2-CH_3-5-i-C_3H_7	C_2H_5	C_2H_5	$C_{16}H_{25}NO$	Oil	75.54	9.88	5.22	77.68	10.19	5.66
2,3,5-$(CH_3)_3$	CH_3	CH_3	$C_{13}H_{19}NO$	87–90	75.79	9.52	6.98	76.05	9.33	6.82
2,3,5-$(CH_3)_3$	C_2H_6	C_2H_5	$C_{15}H_{23}NO$	100–102.5	77.16	9.84	6.11	77.20	9.93	6.00

[a] Lit. m.p., 158° (4).
[b] Phenol darkened rapidly on exposure to air and was converted to more stable carbamate immediately.

atoms were normalized to the smallest whole numbers as measured by the integration of peak areas.

The nitrosophenol produced by a reaction between 2,5-xylenol and nitrous acid gave a spectrum which had methyl doublets centered at 1.97 and 2.16 p.p.m., and coupling constants of 1.3 and 1.6 c.p.s., respectively. The ring protons produced quartettes centered at 6.28 and 7.70 p.p.m., with coupling constants of 1.3 and 1.6 c.p.s., respectively. This is consistent only with the nitroso group in the para position. The isomeric 6-nitroso-2,5-xylenol would have two adjacent ring hydrogen atoms with an expected coupling constant of >6 c.p.s.

The nitrosophenol produced from 2,3-xylenol gave a spectrum which had single methyl peaks at 1.98 and 2.23 p.p.m., and doublets centered at 6.44 and 7.89 p.p.m. with coupling constants of ∼11 c.p.s. The band at 6.44 p.p.m. is characteristic of a ring proton ortho to an oxygen atom and is consistent only with the p-nitroso derivative.

o-tert-Butylphenol gave a nitroso derivative which also had a doublet at 6.46 p.p.m. with a coupling constant of 9.5 c.p.s. This indicates that a ring hydrogen is adjacent to the oxygen atom and is consistent only with the para isomer.

The nitrosophenol produced from 3,5-xylenol (using DMSO as the solvent) gave a spectrum with single bands at 2.37 p.p.m. (methyl groups) and 6.30 p.p.m. (ring hydrogen). Only one type of ring hydrogen and methyl group can be present. This is consistent only with the para isomer, 4-nitroso-3,5-xylenol. The characteristic peak for a ring hydrogen atom ortho to an oxygen atom, 6.25- to 6.50- p.p.m. region, was present in all the compounds.

The Schiff base phenols usually con-

tained a small amount of the corresponding aminophenol starting material as an impurity. This could not be removed satisfactorily by recrystallization techniques. The impurity was relatively insoluble and traces crystallized with the product to give samples with relatively broad melting points.
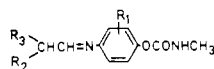
When relatively large amounts of unreacted aminophenol were present, the desired Schiff base phenol could be separated by extraction with hot hexane.

The aminophenol impurity reacted with methyl isocyanate during the final step to give a substituted urea derivative (Equation 6). This material was a

(6)
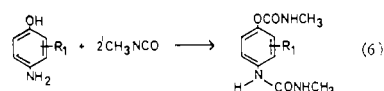
relatively high melting solid which was separated from the carbamates by direct

Table II. Properties and Insecticidal Activity

R_1	R_2	R_3	Molecular Formula	M.P., °C.	Found C	Found H	Found N	Theory C	Theory H	Theory N	MBB LD_{50}	MBB LD_{95}	SAW LD_{50}	SAW LD_{95}
H	CH_3	CH_3	$C_{12}H_{16}N_2O_2$	Oil	63.58	6.92	13.02	65.43	7.32	12.72	100	200	120	300
H	CH_3	n-C_3H_7	$C_{14}H_{20}N_2O_2$	Oil	66.05	7.89	10.89	67.71	8.12	11.28	60	140	230	320
3,5-$(CH_3)_2$	CH_3	CH_3	$C_{14}H_{20}N_2O_2$	80–83	66.79	8.16	11.42	67.71	8.12	11.28	3.2	6	3.2	6
3,5-$(CH_3)_2$	C_2H_5	C_2H_5	$C_{16}H_{24}N_2O_2$	85–89	68.78	8.54	10.05	69.53	8.75	10.14	2.8	3.8	1.0	1.2
3,5-$(CH_3)_2$	CH_3	n-C_3H_7	$C_{16}H_{24}N_2O_2$	Oil	...	...	10.06	...	...	10.14	2.8	4	2.7	3.6
3,5-$(CH_3)_2$	C_2H_5	n-C_4H_9	$C_{18}H_{28}N_2O_2$	Oil	...	...	8.88	...	...	9.20	5.8	8.5	3.0	4.0
2,3-$(CH_3)_2$	CH_3	CH_3	$C_{14}H_{20}N_2O_2$	Glass	...	...	13.96	...	...	11.28	30	45	150	230
3-CH_3-5-C_2H_5	C_2H_5	C_2H_5	$C_{17}H_{26}N_2O_2$	Oil	70.39	8.64	8.86	70.31	9.03	9.65	1.5	2	13	16
3-CH_3-5-C_2H_5	CH_3	n-C_3H_7	$C_{17}H_{26}N_2O_2$	Oil	70.00	8.75	8.96	70.31	9.03	9.65	3.5	4.5	8.8	10
2-CH_3-5-iC_3H_7	C_2H_5	C_2H_5	$C_{18}H_{28}N_2O_2$	Oil	71.20	9.84	9.57	71.02	9.27	9.20	35	63	>500	>500
2,3,5-$(CH_3)_3$	CH_3	CH_3	$C_{15}H_{22}N_2O_2$	Glass	68.63	8.59	10.79	68.67	8.45	10.68	6.4	8.5	34	40
2,3,5-$(CH_3)_3$	C_2H_5	C_2H_5	$C_{17}H_{26}N_2O_2$	Glass	70.74	9.24	9.31	70.31	9.03	9.65	11	15	28	45

[a] Approximate concentration of insecticides in parts per million to give LD for Mexican bean beetles (MBB) and Southern armyworm (SAW).

filtration or by treatment with pentane or hexane. The carbamates were usually oils or glasses which did not crystallize. The various derivatives prepared are summarized in Table II. The structures were verified by means of elementary analysis and an interpretation of their infrared spectra. Strong, sharp bands appeared at the 3.0-, 5.8-, and 6.0-micron regions, which were characteristic of the N—H, C=O, and C=N stretching frequencies, for every carbamate derivative.

Experimental

Insecticidal Test Methods. Primary leaves of Cranberry bean plants, *Phaseoleus vulgaris* L. (var. Cran.), were dipped in aqueous dilutions containing carbamates. The leaves when dry were infested with third instar larvae of the Mexican bean beetle (MBB), *Epilachna varivestis* Muls., or third instar larvae of the Southern armyworm (SAW), *Prodenia eridania* (Cran). The infested plants were caged and held at greenhouse temperatures of about 80° F. for 6 days before making mortality counts. These counts were corrected for natural mortality by the use of Abbott's formula.

Synthesis of Compounds. Each type of reaction will be illustrated with a specific example.

NITROSATION OF PHENOLS. 4-Nitroso - 3,5 - xylenol. Following the method of Karrer and Schlapfer (8), 24 grams of 3,5-xylenol was dissolved in 160 ml. of methanol and diluted with 170 ml. of concentrated HCl. The solution was cooled and maintained at 0° to 5° C. Twenty-two grams of solid sodium nitrite was added in small portions, with agitation, over a 3-hour period. After standing overnight at 5° to 10° C., the heavy slurry was diluted threefold with ice and water, filtered, washed with water and finally pentane, and dried to give 25 grams of yellow solid which melted at 175° C. with decomposition [lit. value, m.p., 173° to 174° C. (*1*)]. Recrystallization from ethanol-water did not appreciably increase the decomposition temperature.

REDUCTION OF NITROSOPHENOLS. 4-Amino-3,5-xylenol. Fifteen grams (0.1 mole) of 4-nitroso-3,5-xylenol (m.p. = 179° C.), 100 ml. of methanol, and 1 gram of 5% Pd on charcoal catalyst were placed in a bomb of a Parr low

pressure hydrogenation apparatus. The required amount of hydrogen, at an initial pressure of 50 pounds, was rapidly absorbed. The warm solution was rapidly filtered to remove the catalyst and the volume of solvent was reduced. Twelve grams of 4-amino-3,5-xylenol crystallized (m.p., 181–83° C.). and was separated by filtration [lit. m.p., 183° to 184° C. (*1*)].

PREPARATION OF AMINOPHENOLS BY COUPLING WITH DIAZOSULFANILIC ACID. 4-Amino-3,5-xylenol (*2*). Solution A was prepared by dissolving 37 grams (0.53 mole) of sodium nitrite in 100 ml. of water. Solution B was prepared by dissolving 95.6 grams (0.50 mole) of sulfanilic acid monohydrate and 26.5 grams (0.25 mole) of sodium carbonate in 500 ml. of water and cooling to 15° C. in an ice bath. Solution C was prepared by mixing 106 ml. of concentrated HCl and 600 grams of ice. Solution D was prepared by mixing 61 grams (0.5 mole) of 3,5-xylenol and 110 grams of NaOH pellets in 600 ml. of water and cooled to 5° C. by the addition of 450 grams of ice.

Solutions A and B were rapidly mixed and then added quickly to C with agitation. The temperature was kept below 15° C. with external cooling. After standing for 20 minutes, the slurry, ABC. was added to D with vigorous stirring. The temperature was kept below 15° C.

After standing for about 2 hours, the brilliant red solution was heated on a hot plate. When the temperature reached 55° C., 230 grams of sodium hydrosulfite was added slowly. The addition was complete when the temperature reached 80° C. At 80° to 85° C. an exothermic reduction suddenly occurred. The temperature rapidly increased to about 95° C. and the color completely disappeared. After cooling to room temperature, 55 grams of 4-amino-3,5-xylenol was separated by filtration (m.p., 178–80° C.).

PREPARATION OF SCHIFF BASES. 4-(2 - Ethylbutylideneamino) - 3 - methyl-5-ethylphenol. Following the method of Clarkson (*3*), 15.1 grams (0.1 mole) of 4-amino-3-methyl-5-ethylphenol was dissolved in 40 ml. of ethanol and then diluted with 40 ml. of water. The temperature was maintained at 50° C. Fifteen grams (0.15 mole) of 2-ethyl-butyraldehyde was added and after 5 minutes, the mixture was rapidly cooled to 0° C. by the addition of ice. The liquid organic phase crystallized, and was separated by filtration, washed with ice water, and placed on a porous dish

to give 29 grams of crude product. Very pale yellow needles were obtained after recrystallization from hexane.

CARBAMATES. 4-(2-Ethylbutylideneamino) - 3,5 - xylyl - *N* - methylcarbamate. Twenty-two grams of 4-(2-ethylbutylideneamino)-3,5-xylenol was dissolved in 100 ml. of methylene chloride and treated with 7 ml. of methyl isocyanate and 5 drops of triethylamine. An exothermic reaction occurred immediately, and an ice bath was used to prevent the temperature from exceeding 28° C. After standing overnight. a small amount of solid was removed by filtration and discarded. The solvent volume was reduced by distillation and the pentane was added. Crystals of crude product appeared (m.p., 75° to 85° C.). One recrystallization from hexane gave 20 grams of product (m.p., 85° to 89° C.).

Literature Cited

(1) Albert, H. E., *J. Am. Chem. Soc.* **76**, 4985 (1954).
(2) Blatt. A. H.. "Organic Syntheses." Coll. Vol. 2, pp. 35, 39, Wiley. New York, 1943.
(3) Clarkson, R. G., U. S. Patent **2,220,065** (Nov. 5, 1940).
(4) Haegele, E.. *Ber.* **25**, 2753 (1892).
(5) Holmes, D. R., Powell, H. M.. *Acta Cryst.* **6**, 256 (1953).
(6) Kaeding. W. W., U. S. Patent **2,984,682** (May 16, 1961).
(7) Kaeding. W. W., Shulgin, A. T., Kenaga, E. E., J. AGR. FOOD CHEM.. **13**, 215 (1965).
(8) Karrer, P., Schlapfer, R.. *Helv. Chim. Acta* **24**, 298 (1941).
(9) Koehler, K., Sandstrom, W., Cordes, E. H.. *J. Am. Chem. Soc.* **86**, 2413 (1964).
(10) Layer, R. L.. *Chem. Revs.* **63**, 489 (1963).
(11) Rodd, E. H.. "Chemistry of Carbon Compounds," Vol. 3A. p. 446, Elsevier, New York. 1954.
(12) Wagner, E. C.. *J. Am. Chem. Soc.* **54**, 660 (1932).